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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,497	LIN ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 3/6/2007. Claims 16-23 are pending. All arguments have been thoroughly reviewed are not found persuasive.

The amendment of claims 17-22 to depend from claim 16 has made the objections to claims 17-22 and the 112-2nd paragraph rejections to claims 17-22 moot.

The amendment of claim 22 to recite glyceraldehyde-3-phosphate dehydrogenase makes the 112-2nd paragraph rejection of this claim moot.

A Final action on claims 16-23 follows.

Newly amended claim 23 is now drawn to the elected invention, and will be examined on the merits. As the previous claim 23 was drawn to a non-elected invention examination of claim 23 will thus require new grounds of rejection necessitated by amendment.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 16, 17, 18, 20, 21, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bauer et al (US Patent 5527898) in view of 1997 HPV compendium, accession number AB027021 GI: 6970427 and Chow et al (Journal of General Virology, 1999, volume 80, pages 2923-2929) and Kino et al (Clinical and Diagnostic laboratory Immunology, 2000, volume 7, pages 91-95) and Hogan et al (US Patent 5541308).

The term "microdots" is not defined in the specification. The claims have been given the broadest reasonable interpretation of microdots as oligonucleotide probes bound to a membrane.

The term "biochip" is not defined in the specification. The claims have been given the broadest reasonable interpretation as drawn to a membrane with oligonucleotide probes fixed to a solid support.

Bauer teaches human papilloma virus (HPV) has been linked to cancer (see column 1, lines 30-32). Bauer teaches different types of HPV have present different risks to affected individuals (see column 1, lines 42-23). Bauer et al teaches a reverse dot blot system to detect HPV (see column 54, example 5). Bauer teaches the membrane bound oligonucleotide probes are fixed in discrete location (see column 54 line 51-52). Bauer teaches probes to the L1 region of HPV (see Table 5 and 5a). Bauer teaches the L1 sequence of HPVs 26, 31, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, and 59 (see SEQ ID NOs 14-20, 273-296). Bauer teaches hybridizing type specific probes to HPV 26, 31, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, and 59 for determining HPV type by hybridization (see column 3 lines 9-16) following amplification with MY11 and MY09 primers. Bauer teaches the type specific probes are 18-20 nucleotides (claim 21) in length with a T_m of 58°C to 64°C (see column 9 lines 15-19). Bauer further teaches the diversity of HPV demonstrates the need for type specific probes (see column 18, lines 45-51). Bauer teaches type specific probes attached to a nylon membrane (claims 18 and 20) (see column 55, line 6). Bauer teaches this approach has led to the discovery of previously unknown or uncharacterized HPV types

(see column 7, lines 46-48). Bauer teaches the identification of new HPV's by his method, require new probes for detection and typing (see column 7, 52-55). Bauer thus teaches the use of a carrier comprising a plurality of microdots to detect and type HPV.

Bauer does not teach detection probes specific to HPV 6, HPV 11,HPV 16, HPV 18, HPV 32, HPV 33, HPV 37, HPV 43, HPV 44, HPV 58, HPV 61, HPV 62, HPV 66, HPV 67, HPV 68, HPV 69, HPV 70, HPV 72, HPV 74, HPV 82, HPV CP8061, HPV CP8034, HPV L1AE5, HPV MM4, HPV MM7 and HPV MM8.

However, the 1997 HPV compendium teaches the L1 sequence of all recited HPVs (see page 15-17), except HPV82 and HPVL1AE5, which are taught by accession number AB027021 GI: 6970427 and Chow et al. The 1997 HPV compendium further teaches the alignment of L1 nucleotide sequences it teaches (see II-L1-23-II-L1-73).

Chow teaches the sequence of HTL7474-S in figure 1b, which is the full length of HPV L1AE5 (see page 2924, second column, lines 8-10). Chow further teaches the screening of DNA from cervical specimens (see page 2923, 2nd column, lines 15-16). Chow further teaches the similarity of HTL7474-S to other highly oncogenic HPV types.

Kino et al teaches the molecular cloning and sequencing of HPV82 (see abstract). Kino et al use of an HPV82 DNA probe (see page 92, 2nd column, lines 6-7). Kino et al teaches any HPV detected by in situ hybridization in invasive cervical carcinoma should be considered high-risk HPV types (see page 91, 1st column, 22-23). Kino et al teaches detection of HPV 82 by in situ hybridization (see figure 1 D). Thus Kino teaches HPV82 is a high risk HPV subtype.

Hogan et al teaches probe design for detection of specific sequences (see abstract). Hogan teaches identification of variable regions (see column 6, lines 3-55). Hogan teaches that the target sequences should be aligned in the variable regions (see column 6 line 67—column 7, line 8) to identify probe regions. Hogan further teaches probes should be positioned to minimize stability of probe: nontarget hybrids, by avoiding GC rich regions of homology to non-target organisms and areas of mismatch (see column 7 lines 10-15). Hogan further teaches maximizing stability of the probe target hybrid, by avoiding long AT sequences and terminating hybrids with G: C base pairing and by designing probes with the appropriate T_m (see column 7 lines 16-19). Hogan teaches probes designed from these methods allow organisms to be distinguished from phylogenetic neighbors (column 2 lines 38-39) with accuracy, simplicity, economy and speed (column 3, lines 4-6)

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to the improve Bauer's method of HPV detection and typing to include HPV 6, HPV 11, HPV 16, HPV 18, HPV 32, HPV 33, HPV 37, HPV 43, HPV 44, HPV 58, HPV 61, HPV 62, HPV 66, HPV 67, HPV 68, HPV 69, HPV 70, HPV 72, HPV 74, HPV 82, HPV CP8061, HPV CP8034, HPV L1AE5, HPV MM4, HPV MM7 and HPV MM8 taught in the 1997 HPV compendium and accession number AB027021 GI: 6970427 and Chow et al (Journal of General Virology, 1999, volume 80, pages 2923-2929). The ordinary artisan would be motivated to improve Bauer's method, because Bauer teaches HPV has been linked with cancer and the risk associated with each subtype is different. The ordinary artisan would further be motivated to include the

HPV types taught by the 1997 HPV compendium, accession numbers, and Chow, because Bauer teaches the need to make probes and distinguish HPV types. Further, Chow and Kino both teach on the oncogenic potential of different HPV subtypes and the use of probes for their HPV of interest. The ordinary artisan would be motivated to align the L1 region of HPV types and make probes for HPV 6, HPV 11, HPV 16, HPV 18, HPV 26, HPV 31, HPV 32, HPV 33, HPV 35, HPV 37, HPV 39, HPV 42, HPV 43, HPV 44, HPV 45, HPV 51, HPV 52, HPV 53, HPV 54, HPV 55, HPV 56, HPV 58, HPV 59, HPV 61, HPV 62, HPV 66, HPV 67, HPV 68, HPV 69, HPV 70, HPV 72, HPV 74, HPV 82, HPV CP8061, HPV CP8034, HPV L1AE5, HPV MM4, HPV MM7 and HPV MM8, because Hogan teaches alignment allows probe design maximize homology to target sequences and minimize homology to non-target sequences (see column 7 lines 3-8). The ordinary artisan would be motivated to align the L1 sequences of recited HPV types because Hogan teaches alignment allows probe design maximize homology to target sequences and minimize homology to non-target sequences. The ordinary artisan would further be motivated to align this region because Hogan teaches alignment of variable regions of DNA is a step in probe design. The ordinary artisan would be motivated by the teachings Bauer, the 1997 HPV compendium, AB027021 GI: 6970427, and Chow et al and Hogan to make probes specific to the HPV recited including probes with SEQ ID NO listed in claim 17. IT is noted that, Blast searches done with the probes in claim 17 possessed 100% identity with the sequences taught by the 1997 HPV compendium, Bauer, Chow, and accession number cited.

Designing probes, which are equivalents to those taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes, see Hogan. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of probes drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design probes. As discussed above, the ordinary artisan would be motivated to have designed and tested new probes to obtain additional oligonucleotides that function to detect specific HPV subtypes and identify oligonucleotides with improved properties. The ordinary artisan would have a reasonable expectation of success of obtaining additional probes from within the alignment provided by the 1997 HPV compendium, Chow et al, and sequence of accession numbers AB027021 GI: 6970427. Thus, for the reasons provided above, the ordinary artisan would have designed additional probes using the teachings in the art at the time the invention was made. The claimed SEQ ID NOs are obvious over the cited prior art, absent secondary considerations.

Response to Arguments

Newly amended claim 23 has been rejected as obvious in the instant rejection.

The papers filed on 3/6/2007 correctly assert on page 15, that Bauer teaches the amplification primers of Bauer are directed to HPV types 6, 11, 16, 18 and 33, which have high sequence homology in the L1 region. The response further incorrectly asserts that due to the amplification primers being directed to the sequences of HPV

types 6, 11, 16, 18 and 33, that Bauer does not teach probes to detect HPV 6, 11, 16, 18, and 33. These arguments have been fully been considered but are not found persuasive because Bauer teaches probes specific for HPV 6, 11, 16, 18, and 33 (see Table 2; table 5, table 8). Further Bauer teaches the use of primers based on HPV types 6, 11, 16, 18 and 33 for the amplification of the L1 region, it does not preclude detection of this region, contrary Bauer's invention is based on amplification of the L1 region of HPV for detection by probes to this area and tables 2, 5, and 8 teach probes for the detection of HPV types 6, 11, 16, 18, and 33.

The response of 3/6/ 2007, further asserts that the Bauer teaches detection probes are designed to avoid sequence that hybridize to the genomic sequences of HPV types 6, 11, 16, 18 and 33. The response points to the negative limitation in claims 1-50 as the basis for this argument. This argument has been fully considered but is not found persuasive because Bauer specific teaches probes to the L1 region of HPV types 6, 11, 16, 18 and 33 in tables 2, 5, and 8. Bauer thus does not teach avoiding these sequences. Further, Bauer specifically teaches, "the present method is applicable to any human papilloma virus, and is especially preferred for detecting and typing genital HPVs. The method can be used to detect isolate-to-isolate variation within a particular HPV type and can also be used to screen for significant changes in HPVs present in a patient" (column 11, lines 47-52). Thus Bauer suggests the combination of his method with any HPV sequence for detection of the HPV types. This explicit teaching by Bauer suggests that detection of other HPV types would be obvious. Further Bauer teaches that probes that hybridize to all HPV types are useful for

detection if amplification has occurred (see column 8, lines 25-31). Thus Bauer not only teaches probes to HPV types 6, 11, 16, 18 and 33 and suggests that his method can be used to identify any HPV, he further teaches inclusion of probes to all HPVs would serve as a control for amplification.

The 3/6/2007 response asserts on page 15, that Bauer discloses how to detect 15 HPVs and further asserts Bauer's states that the detector cannot attach a large number of probes at column 10, lines 6-9. This argument has been fully considered but is not found persuasive because the applicant is directing arguments to Bauer's embodiment of using a microwell plate as the solid support. First it is noted that Bauer's microwell plates is a 96 well plate (see column 55, line 67), which would be easily able to have the 39 probes of the instant invention. Further Bauer et al teaches the use of probes spotted on a membrane for the detection of HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 51, 52, 53, 54, 55, 56, 57, 58, 59, 68 and clinical samples P88, P155, P238A, P291 and W13B, which is 26 probes, thus it would be obvious to one of skill in the art to add 13 more probes to the membrane or use all 96 wells of the microwell plate (column 53, lines 19-21). Further, Bauer teaches the use of a reverse dot blot where a large number of different probes are to be used (see column 9, lines 45-60). Thus Bauer does teach a detector capable of detecting 39 HPV types.

The papers filed on 3/6/2007 further asserts Bauer discloses probes that generally have less than 75% similarity, which allows for " a good deal of cross hybridization"(column 9, lines 15-19). These arguments appear to suggest that probes of Bauer are not able to distinguish highly similar sequences. These arguments have

been fully considered but are not found persuasive because although Bauer suggests that the probes can be up to 75% similar, but Bauer teaching are not limited to probes that are 75% similar. Bauer et al teaches HPV6 probe (SEQ ID NO 142 CATCCGTAACTACATCTTCAA), which has no apparent similarity to HPV11 probe (SEQ ID 147 TCTGTGTCTAAATCTGCTACA) (see table 5). Bauer et al further teaches the use of sequence specific oligonucleotides and stringent hybridization conditions wherein hybridization is exactly complementary to the sequence being detected (see column 4, lines 30-37). Bauer further teaches, "relaxing stringency of hybridizing condition will allow sequence mismatches to be tolerated" (see column 4, lines 49-50). Bauer thus inherently teaches his method does not allow mismatches or cross hybridization. Bauer further suggests this method allows, "detect and isolate to isolate variation within a particular HPV type and can also be used to screen for significant changes in HPVs present in a patient." Bauer further teaches cross-hybridization can be minimized by increasing the stringency of washing (see column 16, lines 10-11). As Bauer teaches that this method allows for the detection of variations within a subtype, which are inherently has small difference in nucleic acid sequence, Bauer thus teaches probes that do meet the claim limitations and does in combination with 1997 HPV compendium, Chow et al, accession number, AB027021 GI: 6970427 and Hogan make the instant claims obvious.

The papers filed on 3/6/20078 further assert that due to the sequence similarity of HPVL1AE5 with those of HPV 18, 39, 45, 59, 68, and 70 that the combined teachings of Chow and Bauer. As discussed in the immediately proceeding paragraph Bauer's

method with discriminate a single nucleotide difference and thus will discriminated the L1 gene with 78% similarity.

The response further asserts that Hogan's invention is specifically drawn to non-viral DNA target probes to distinguish rDNA. These assertions are correct, however Hogan does teach specific methods and rationale for the design of probes based a sequence alignment as stated in the first action on the merits. These methods are applicable to all nucleic acid sequence irrespective of the source viral, bacterial, mammalian, etc. Hogan's method specifically describes how to design probes that based on variable regions of DNA, avoiding GC rich regions and AT regions as they adversely affecting Tm and hybridization. Hogan teaches probes designed by these methods allow organisms to be distinguished from phylogenetic neighbors. Thus although Hogan's teachings are directed to non-viral DNA targets they are equally applicable to the detection of the variable regions of viral DNA including HPV L1.

The explicit teachings of Bauer, "the present method is applicable to any human papilloma virus, and is especially preferred for detecting and typing genital HPVs. The method can be used to detect isolate-to-isolate variation within a particular HPV type and can also be used to screen for significant changes in HPVs present in a patient" (column 11, lines 47-52), suggest the instant invention is obvious over Bauer et al, 1997 HPV compendium, accession number AB027021 GI: 6970427, Chow et al, Kino et al, and Hogan. Thus this rejection is maintained.

4. Claims 19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bauer et al (US Patent 5527898), 1997 HPV compendium, Chow et al, accession

number AB027021 GI: 6970427 and Hogan et al (US Patent 5541308) as applied to claims above 16-18, 20, and 21, and further in view of Lockhart et al (US Patent 6040138).

The teachings of Bauer et al (US Patent 5527898), 1997 HPV compendium, Chow et al, accession number AB027021 GI: 6970427 and Hogan et al (US Patent 5541308) are set forth above. Bauer et al, 1997 HPV compendium, Chow et al, accession number, AB027021 GI: 6970427 and Hogan et al do not teach the use of GAPDH as a control or glass as a carrier.

However, Lockhart et al teaches the use of glass as a support for an array of oligonucleotides (see column 19, lines 48-50) because glass allows direct synthesis of oligonucleotides on the solid support. Lockhart further teaches the use of GAPDH as constitutively expressed gene for normalization controls (see column 16, lines2-5 and 55-60).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to improve HPV detection method of Bauer et, 1997 HPV compendium, Chow et al, accession number AB027021 GI: 6970427 and Hogan et al by using the glass support and GAPDH controls of Lockhart, because Lockhart teaches the glass support allows probe synthesis on the array and GAPDH probes allow normalization of data. The ordinary artisan would be motivated to use the glass support of Lockhart, because Lockhart teaches it allows oligonucleotide synthesis on the support. The ordinary artisan would be motivated to use GAPDH as a control, because Lockhart teaches GAPDH allows normalization of controls.

Response to Arguments

The response of 3/6/2007 on page 17 asserts that Lockhart does not cure the deficiencies previously addressed and does not provide motivation to arrive at the claimed invention. These arguments have been thoroughly reviewed, but are not found persuasive because as discussed with respect to claims 16-18, 20-21, and 23 the teachings of Bauer et al, 1997 HPV compendium, accession number AB027021 GI: 6970427, Chow et al, Kino et al, and Hogan et al do meet each and every limitation of the claims. Further the first office action suggests that the ordinary artisan would be motivated to use the glass support because Lockhart teaches it allows oligonucleotides to be synthesized directly on the support. The first action on the merits further suggests that the ordinary artisan would be motivated to use GAPDH as a control, because Lockhart teaches it allows normalization of controls. Thus the combination of Bauer et al, 1997 HPV compendium, accession number AB027021 GI: 6970427, Chow et al, Kino et al, Hogan, and Lockhart do provide motivation and teachings for all the limitations of the claims. Thus this rejection is maintained.

Summary

No claims are allowed over prior art cited.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

JEANNINE A. GOLDBERG
PRIMARY EXAMINER
5/23/07